Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop
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Session 4

1. Topic and Author

Clinical trials of HRT for secondary prevention.
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

In the Heart Estrogen/Progestin Replacement Study (HERS), 2,763 postmenopausal women with documented coronary disease were randomized to CEE 0.625 mg/day + continuous MPA 2.5 mg/day or placebo and were followed for 4.1 years.[1] No difference was seen for the primary endpoint, coronary death + nonfatal MI, but in the first year an excess of coronary events was present in the active HRT group. Extensive post hoc analyses did not identify any subgroup of HERS participants in which HRT was clearly beneficial or harmful,[2] although women with high Lp(a) levels may have obtained benefit, and women with lower levels harm.[3] Long term follow-up of the HERS population revealed no benefit of extended therapy,[4] with an increased risk of venous thrombo-embolism and biliary tract surgery, and statistically non-significant increases in breast cancer and total mortality.[5]

In the Estrogen Replacement and Atherosclerosis (ERA) Trial, 309 women with coronary disease were randomized to estrogen, estrogen + MPA, or placebo.[6] Coronary arteriography was done at baseline and after a mean follow-up of 3.2 years and progression of coronary atherosclerosis was assessed by quantitative methods. No differences were found among the 3 groups for changes in minimum lumen diameter, the primary endpoint, or for any of the other angiographic or clinical endpoints.

Two trials have assessed the effects of 17ß-estradiol on carotid intimal media thickness. In the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), 222 postmenopausal women were randomized to 2 years of treatment with micronized 17ß-estradiol or to placebo. Although the results have not yet been published, the 17ß-estradiol group was reported to have improved carotid measurements.[7] On the other hand, the Postmenopausal Hormone Replacement against Atherosclerosis (PHOREA) Trial found no effect of 17ß-estradiol combined with either of two doses of a progestin on carotid intimal media thickness in a study of 321 postmenopausal women followed for one year.[8]

The Papworth HRT and Atherosclerosis Survival Enquiry (PHASE) included 255 postmenopausal women with coronary disease randomized to transdermal 17ß-estradiol, with or without cyclic norethisterone.[9] The trial was stopped early because of the likelihood that it would not show benefit. The primary endpoint, death, MI, or unstable angina occurred more often in the hormone group (hazard ratio 1.23, 95% CI 0.82-1.86).

Based upon these trials, it seems reasonable to conclude that HRT does not prevent recurrent coronary events in postmenopausal women with documented coronary disease, and probably increases the risk during the first year of treatment. The most commonly used HRT preparation in these trials was CEE 0.625 mg/day + MPA 2.5 mg/day. It is possible that smaller doses, different HRT preparations, or different routes of delivery might yield different results. Outcome data are not yet available for SERMS such as roloxifene.

Women who have participated in the secondary prevention trials of HRT have a high incidence of diabetes, obesity and hypertension compared to men with coronary disease. Diabetes, smoking and hypertension are even more prevalent among women with coronary disease not participating in clinical trials, as shown by a comparison of HERS and NHANES III women.[10] The prevalence of diabetes and obesity is increasing in women at risk for coronary disease, and smoking rates in young women have either not declined or are increasing.

3. Current challenges and the most important issues for future research

It may be worthwhile to test other HRT formulations or other dosages in randomized trials. This process would be facilitated if a reliable surrogate endpoint were available. The role of raloxifene in secondary prevention is being evaluated in an ongoing trial. Understanding how HRT increases early risk and finding a way to prevent it would increase the safety of HRT for other indications, specifically hot flashes.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

The message that HRT is not of benefit for cardiovascular protection should be coupled to the message that other effective treatments are available. For example, women in HERS who took statins had a reduction in coronary events.[11]

5. Translating new findings to improved diagnosis and treatment/saving lives.

The available primary and secondary prevention trials of HRT should convince practitioners to stop prescribing E+P for coronary prevention. Their focus should shift to therapies of proven benefit in women with coronary disease: aspirin, ß-blockers, ACE inhibitors and statins. These drugs are currently underprescribed, and adherence to prescribed treatment has been documented to be poor. Improvements in this area would save lives and prevent coronary events.

6. References.

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